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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/495, 31/50, 31/44, 31/445</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/40140</b> <b>(43) International Publication Date:</b> 19 December 1996 (19.12.96)
<b>(21) International Application Number:</b> PCT/US96/09561 <b>(22) International Filing Date:</b> 5 June 1996 (05.06.96) <b>(30) Priority Data:</b> 08/474,072 7 June 1995 (07.06.95) US 08/653,905 28 May 1996 (28.05.96) US <b>(71) Applicants:</b> GUILFORD PHARMACEUTICALS INC. [US/US]; 6611 Tributary Street, Baltimore, MD 21224 (US). JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE [US/US]; Suite 72-100, 2024 East Monument, Baltimore, MD 21205 (US). <b>(72) Inventors:</b> STEINER, Joseph, P.; 988 Sugar Maple Street, Hampstead, MD 21074 (US). SNYDER, Solomon; Johns Hopkins Medical School, 725 N. Wolfe Street, Baltimore, MD 21205-2185 (US). HAMILTON, Gregory, S.; 6501 Frederick Road, Catonsville, MD 21228 (US). <b>(74) Agent:</b> NATH, Gary, M.; Nath & Associates, 1835 K Street, N.W. #750, Washington, DC 20006-1203 (US).	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>With amended claims.</i>	
<b>(54) Title:</b> INHIBITORS OF ROTAMASE ENZYME ACTIVITY <b>(57) Abstract</b> <p>This invention relates to the method of using neurotrophic pipecolic acid derivative compounds having an affinity for FKBP-type immunophilins as inhibitors of the enzyme activity associated with immunophilin proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity to stimulate or promote neuronal growth or regeneration.</p>		

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exist in a complex with FKBP-12. Dissociation of FKBP-12 from these complexes causes the calcium channel to become "leaky" (Cameron et. al., 1995) Calcium fluxes are involved in neurite extension so that the IP-3 receptor and the  
5 ryanodine receptor might be involved in the neurotrophic effects of drugs. Since the drugs bind to the same site on FKBP-12 as the IP-3 receptor or the ryanodine receptor, one would have to postulate that the drugs displace the channels from FKBP-12. No interaction between these calcium channels  
10 in cyclophilin has been reported so that this model would not explain the neurotrophic actions of cyclosporin A.

The neurotrophic actions of the drugs studied here are exerted at extremely low concentrations indicating potencies comparable to those of neurotrophic proteins such as brain  
15 derived growth factor, neurotrophin-3 and neurotrophic growth factor.

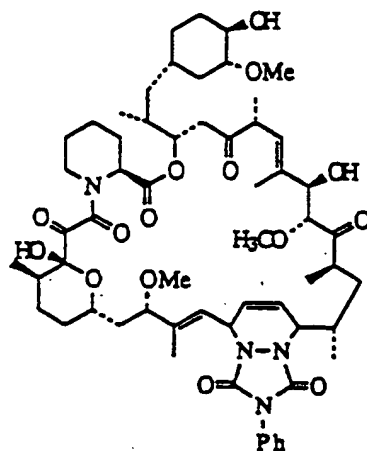
The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All polymer molecular  
20 weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.

Illustrative pipecolic acid derivative compounds which  
25 can be used for the purposes of this invention include:

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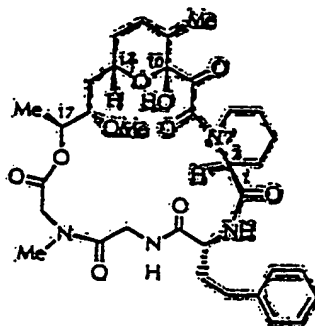
## EXAMPLE 1



Way-124,466

This exemplary pipecolic acid derivative compound is disclosed by Ocain et al., *Biochemical and Biophysical Research Communications*, Vol. 192, No. 3, 1993. The compound was synthesized at Wyeth-Ayerst by Dr. Phil Hughes by reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with rapamycin.

## EXAMPLE 2

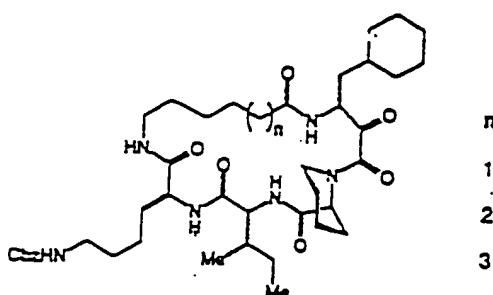


RAP-Pa

47

This pipecolic acid derivative compound is disclosed by Chakraborty et al., *Chemistry and Biology*, March 1995, 2:157-161.

## EXAMPLES 3-5

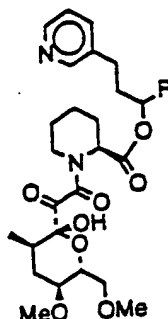


5 Exemplary pipecolic acid derivative compounds are disclosed by Ikeda et al., *J. Am. Chem. Soc.* 1994, 116, 4143-4144, and are incorporated herein by reference.

## EXAMPLES 6-9

10 Exemplary pipecolic acid derivative compounds are disclosed by Wang et al., *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, No. 9, pp. 1161-1166, 1994, particularly compounds 2a-2d and are incorporated herein by reference.

## EXAMPLE 10



This exemplary pipecolic acid derivative, compound 10, is disclosed by Birkenshaw et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 21, pp. 2501-2506, 1994, and is incorporated herein by reference.

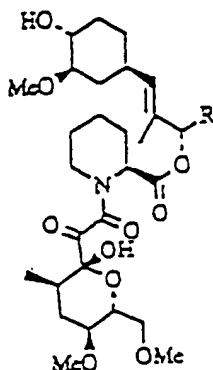
## EXAMPLES 11-21

Exemplary pipecolic acid derivative compounds are disclosed by Holt et al., *J. Am. Chem. Soc.*, 1993, 115, 9925-9938, particularly compounds 4-14, and are incorporated herein by reference.

## EXAMPLES 22-30

Exemplary pipecolic acid derivative compounds are disclosed by Caffery et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 21, pp. 2507-2510, 1994, and are incorporated herein by reference.

### EXAMPLE 31



This exemplary pipecolic acid derivative, compound 31, is disclosed by Teague et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 3, No. 10, pp. 1947-1950, 1993 and is incorporated herein by reference.

EXAMPLES 32-34

Exemplary pipecolic acid derivative compounds are disclosed by Yamashita et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4., No. 2, pp. 325-328, 1994, particularly, compounds 11, 12, and 19, and are incorporated herein by reference.

**EXAMPLE 35-55**

Exemplary pipecolic acid derivatives are disclosed by Holt et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 2, pp. 315-320, 1994, particularly, compounds 3-21, and 23-24, and are incorporated herein by reference.

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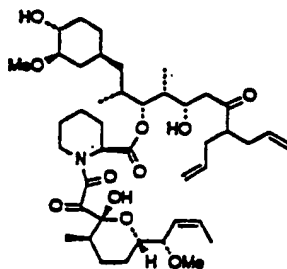
## EXAMPLES 56-68

Exemplary pipecolic acid derivative compounds are disclosed by Holt et al., *Bioorganic & Medicinal Chemistry Letters*, Vol. 3, No. 10, pp. 1977-1980, 1993, particularly compounds 3-15 and are incorporated by reference herein.

## EXAMPLES 69-83

Exemplary compounds of the present invention are disclosed by Hauske et al., *J. Med. Chem.* 1992, 35, 4284-4296, particularly compounds 6, 9-10, 21-24, 26, 28, 31-32, and 52-55, and are incorporated herein by reference.

## EXAMPLE 84



## SLB506

This exemplary pipecolic acid derivative is disclosed by Teague et al., *Bioorganic & Med. Chem. Letters*, Vol. 4, No. 13, pp. 1581-1584, 1994, and is incorporated herein by reference.

51

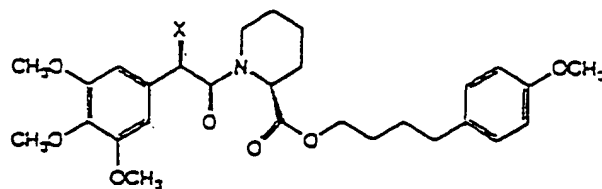
**EXAMPLES 85-88**

Exemplary pipecolic acid derivative compounds are disclosed by Stocks et al., *Bioorganic & Med. Chem. Letters*, Vol. 4, No. 12, pp. 1457-1460, 1994, particularly compounds 2, 15-17 and are incorporated herein by reference.

**EXAMPLES 90-111**

Additional exemplary pipecolic acid derivatives are described in Scheme 10, Tables 1-5.

SCHEME 01

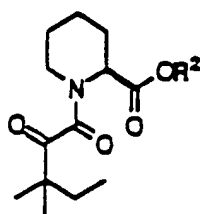


EXAMPLE/COMPOUND	STRUCTURE
6	X = H <sub>2</sub>
7	X = CH <sub>2</sub>
8	X = H, CH <sub>3</sub>
9	X = O

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## SCHEME 2



## EXAMPLE/COMPOUNDS No.

R<sub>2</sub>

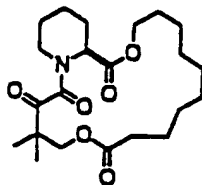
	11	
	12	
5	13	
	14	
	15	
	16	
	17	
10	18	

## SCHEME 3

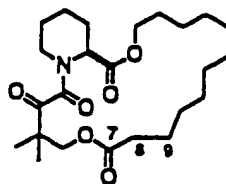
EXAMPLE/COMPOUND No.

STRUCTURE

19

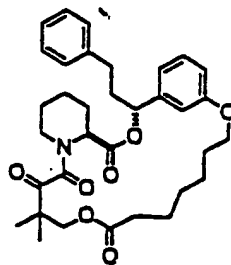


20



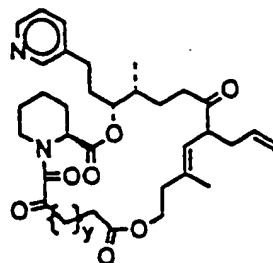
5

21



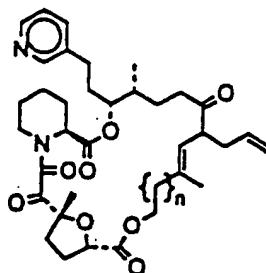
Scheme 4

Table 1



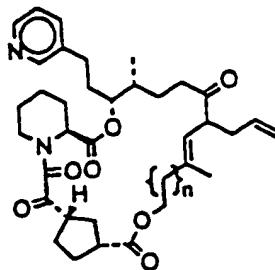
Example/Compound No.	Structure
24	y=1
23	y=2
24	y=3

Table 2



Example/Compound No.	Structure
25	n=1
26	n=2
27	n=3

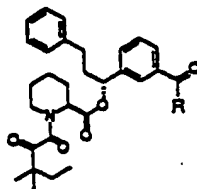
Table 3.



Example/Compound No.	Structure
28	n=1
29	n=2
30	n=3

5

SCHEME 5



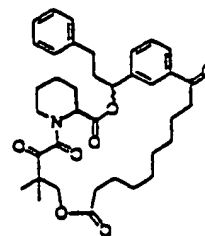
EXAMPLE/COMPOUND No.

STRUCTURE

32  
33R=phenyl  
R=N(allyl)<sub>2</sub>

10

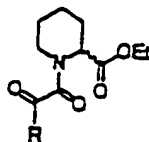
34



56

## Scheme 6

Table 1



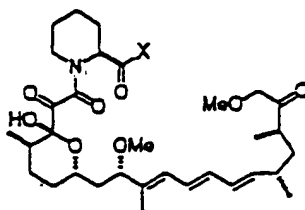
Example/Compound No.		Structure R
5	35	
	36	
	37	
	38	
	39	
10	40	
	41	
	42	
	43	
15	44	
	45	
	46	
	47	
	48	
	49	
20	50	



58

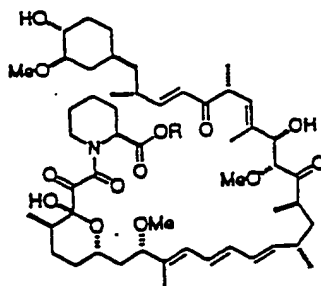
## SCHEME 7

TABLE 1



	56	x = OH
	57	x = OMe
5	58	x = Oi Pr
	59	x = OBn
	60	x = OCH MePh
	61	x = OCH <sub>2</sub> CHCHPh
	62	x = OCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> (3, 4-OMe <sub>2</sub> ) Ph
10	63	x = NHBn
	64	x = NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> Ph

Table 2



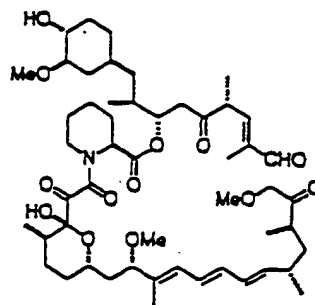
65	R = Me
66	R = Bn

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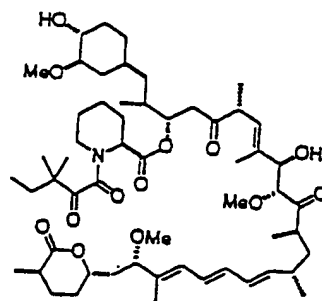
59

Table 3

67



68



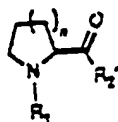
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60

## Scheme 8

Table 1



Example/Compound No.

Structure

69



5

 $R_2 = \text{Phe-o-tert-butyl}$ 

70

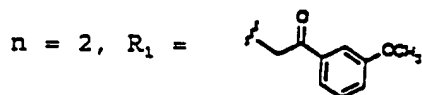
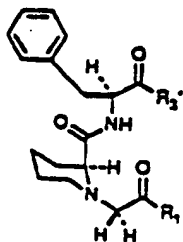
 $R_2 = \text{Phe-o-tert-butyl}$ 

Table 2



10

71

 $R_1 = m\text{-OCH}_3\text{Ph}; R_2 = \text{Val-o-tert-butyl}$ 

72

 $R_1 = m\text{-OCH}_3\text{Ph}; R_2 = \text{Leu-o-tert-butyl}$ 

73

 $R_1 = m\text{-OCH}_3\text{Ph}; R_2 = \text{Ileu-o-tert-butyl}$ 

74

 $R_1 = m\text{-OCH}_3\text{Ph}; R_2 = \text{hexahydro-Phe-o-tert-butyl}$ 

15

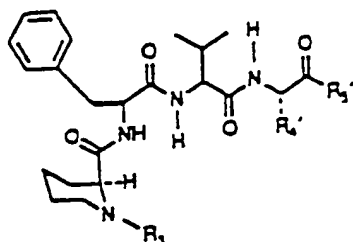
75

 $R_1 = m\text{-OCH}_3\text{Ph}; R_2 = \text{allylalanine-o-tert-butyl}$ 

76

 $R_1 = \text{B-naphthyl}; R_2 = \text{Val-o-tert-butyl}$

Table 3



Example/Compound No.

Structure

77

 $R_1 = \text{CH}_2(\text{CO}) - m\text{-OCH}_3\text{Ph}$  $R_{4,1} = \text{CH}_2\text{Ph}$  $R_{5,1} = \text{OCH}_3$ 

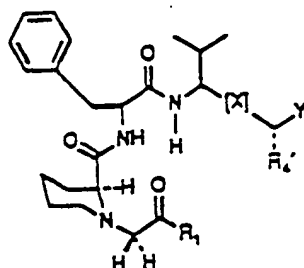
5

78

 $R_1 = \text{CH}_2(\text{CO}) - 3\text{-naphthyl}$  $R_{4,1} = \text{CH}_2\text{Ph}$  $R_{5,1} = \text{OCH}_3$ 

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Table 4



Example/Compound No.	Structure
5	79 $R_1 = m\text{-OCH}_3\text{Ph}$ $X = \text{trans-CH=CH}$ $R_{4^1} = \text{H}$ $Y = \text{OC(o)Ph}$
10	80 $R_1 = m\text{-OCH}_3\text{Ph}$ $X = \text{trans-CH=CH}$ $R_{4^1} = \text{H}$ $Y = \text{OC(o)CF}_3$
15	81 $R_1 = m\text{-OCH}_3\text{Ph}$ $X = \text{trans-CH=CHI}$ $R_{4^1} = -$ $Y = -$
15	82 $R_1 = m\text{-OCH}_3\text{Ph}$ $X = \text{trans-CH=CH}$ $R_{4^1} = \text{H}$ $Y = \text{OCH}_2\text{CH=CH}_2$
20	83 $R_1 = m\text{-OCH}_3\text{Ph}$ $X = \text{C=O}$ $R_{4^1} = \text{H}$ $Y = \text{Ph}$

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Scheme 9

Table 1

85

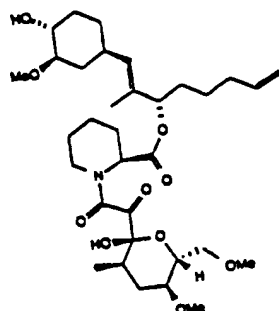
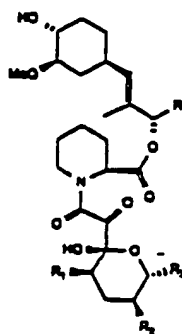


Table 2



5

86

 $R_1 = H, R_2 = OMe, R_3 = CH_2OMe$ 

87

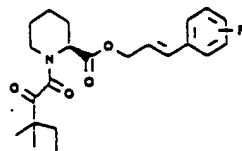
 $R_1 = H, R_2 = R_3 = H$ 

88

 $R_1 = Me, R_2 = R_3 = H$

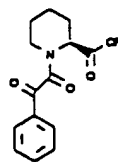
## Scheme 10

Table 1



	Example	R =
5	90	3,4-dichloro
	91	3,4,5-trimethoxy
	92	H
	93	3-(2,5-Dimethoxy)-phenylpropyl
10	94	3-(3,4-Methylene-dioxy)phenylpropyl

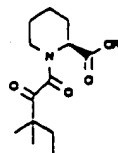
Table 2



	Example	R =
15	95	4-(p-Methoxy)-butyl
	96	3-Phenylpropyl
	97	3-(3-Pyridyl)-propyl

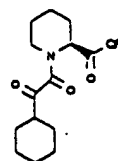
65

Table 3



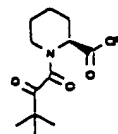
	Example	R =
	98	3-(3-Pyridyl)-propyl
	99	1,7-Diphenyl-4-heptyl
5	100	4-(4-Methoxy)butyl
	101	1-Phenyl-6-(4-methoxy-phenyl)-4-hexyl
	102	3-(2,5-Dimethoxy)phenyl-propyl
10	103	3-(3,4-Methylenedioxy)-phenylpropyl
	104	1,5-Diphenylpentyl

Table 4



15	Example	R =
	105	4-(4-Methoxy)butyl
	106	3-Cyclohexylpropyl
	107	3-Phenylpropyl

Table 5



20

	Example	R =
	108	3-Cyclohexylpropyl
	109	3-Phenylpropyl
	110	4-(4-Methoxy)butyl
25	111	1,7-Diphenyl-4-heptyl

## NEUROTROPHIC EFFECTS OF ROTAMASE INHIBITORS

Table I lists a number of the claimed examples together with their potencies to induce trophic effects in cultured sensory neurons, as described above.

5 Figures 19 and 20 show photomicrographs of Example 111 and Example 17 promoting neurite outgrowth in the dorsal root ganglion cultures.

Table I  
In Vitro Potencies of Test Examples

10	Example	Rotamase Inhibition $K_i$ , nM	Neutrophic $ED_{50}$ Chick DRGs, nM
	6	140	25
	9	13	0.030
	11	170	1
15	12	250	300
	13	25	80
	15	17	0.30
	19	12	0.017
	36	>10,000	>10,000
20	41	1300	5000
	50	>10,000	>10,000
	90	1800	2500
	91	28	200
	92	39	90
25	93	75	35
	94	70	8
	95	165	5-10
	96	740	10-20
	97	725	150
30	98	130	75
	99	30	5
	100	60	43
	101	15	0.17
	102	12	2.5
35	103	120	3
	104	20	.016
	105	103	6
	106	760	1
	107	210	0.82
40	108	32	0.29
	109	2	0.08
	110	24	0.002
	111	5	0.08

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